

REMARKS

Claims 73-104 are pending. Claims 73-74, 76, 80-84 and 86 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Publication No. 2003/0104030 to Igaki in view of U.S. Patent No. 6,251,136 to Guruwaiya. Claims 75, 99-101 and 104 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of Guruwaiya. Claims 73-74, 76-78, 80-82, 86, 88-89, 91-93 and 98 stand rejected under 35 U.S.C. §103(a) as being unpatentable over European Patent No. EP 0405284 to Greiner. Claims 75, 90 and 99-104 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner in view of Guruwaiya. Claim 79 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of U.S. Patent No. 6,670,398 to Edwards. Claims 79 and 95 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner in view of Edwards. Claim 85 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of PCT Publication WO 01/87368 to Mehta. Claims 85 and 97 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner in view of Mehta. Claim 87 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of U.S. Patent No. 6,299,604 to Ragheb. Claim 87 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner in view of Ragheb. Claims 81, 83-84, 86, 93-94, 96 and 98 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner in view of Igaki.

Applicants have amended independent Claims 73, 88 and 99 for clarification. Applicants have also amended dependent Claims 75, 82, 85, 86, 87, 90, 97 and 98 for clarification. Applicants respectfully traverse the §103 rejections for the reasons set forth below.

Independent Claim 73

Independent Claim 73 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of Guruwaiya. Independent Claim 73 also stands rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner.

Amended independent Claim 73 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

- immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises *non-layered* polymeric material;
- pressurizing the mixture of carrier fluid and pharmacological agent for a time sufficient to cause the carrier fluid and pharmacological agent to at least partially penetrate the *non-layered* polymeric material;
- removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the *non-layered* polymeric material and the pharmacological agent becomes elutably trapped within the *non-layered* polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the *non-layered* polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Igaki fails to teach or suggest a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient. In fact, the Action concedes that Igaki fails to teach a drug elutably trapped within polymeric material in a predetermined concentration gradient. (Action, Page 3). However, the Action states that "Igaki teaches that the pressure is gradually exhausted (i.e., under controlled conditions) and, thus, teaches all the steps as claimed." (Action, Page 3). The Action then concludes that, "because the method of Igaki is so similar to the claimed steps, the two methods must necessarily achieve similar results." (Action, Page 3). Applicants respectfully disagree.

Igaki describes controlling the release time point and quantity of an impregnated drug, not via a concentration gradient, but via the use of layers of biodegradable polymer material. Igaki specifically states "by providing the layer(s) of the drug-containing biodegradable polymer in this manner, one or more drugs may be impregnated in the stent, and it is possible to permit more strict control of the drug releasing time point or the quantity of the released drug, or different drugs can be released at the desired same time point." (Igaki, Para. 0072). Igaki also describes retarding the rate of release of a drug impregnated in a stent

via the use of a layer of biodegradable polymer material not containing a drug. (Igaki, Para. 0073).

One skilled in the art would not, upon reading Igaki, produce a non-layered stent with a drug concentration gradient in the stent material. To the contrary, one skilled in the art, upon reading Igaki, would use various layers to accomplish what Applicants accomplish via a concentration gradient. The fact that Igaki utilizes layers to control the time of drug release and the quantity of drug release illustrates that Igaki does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

The secondary reference, Guruwaiya, fails to rectify the deficiencies of primary reference, Igaki. Guruwaiya describes a method for coating a stent that requires the sequential application of three layers of different materials onto a stent's surfaces. A first layer is applied to all or to selected surfaces of a stent and serves as a base or primer coat which readily adheres to the material of which the stent is constructed and in turn, is able to attract and retain the subsequently applied pharmacological agent. Such pharmacological agent, in the form of dry, micronized particles is dusted directly onto all or onto only selected surfaces of the base layer coated stent to form a second layer. A membrane forming polymer is subsequently applied over the coated stent surfaces wherein such polymer is selected for its ability to permit the diffusion of the pharmacological agent therethrough. (Col. 2, Lines 21-34). The amount of pharmacological material deposited in the second layer determines the total dosage that can delivered while the thickness of the top layer determines the rate of delivery. (Col. 2, Lines 45-48). Thus, Guruwaiya does not teach or suggest producing a non-layered stent with a drug concentration gradient elutably trapped within the stent material. Furthermore, the fact that Guruwaiya utilizes a layer to control the rate of drug delivery illustrates that Guruwaiya does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

Accordingly, Igaki and Guruwaiya, alone or in combination, fail to teach or suggest all of the recitations of independent Claim 73. Applicants respectfully assert that the rejections of independent Claim 73, and all claims depending therefrom, under 35 U.S.C. §103 are overcome.

The other primary reference, Greiner, cited by the Action, also fails to teach or suggest a drug elutably trapped within polymeric material in a predetermined concentration gradient. Greiner describes a method of impregnating a catheter, made of polymeric material, with a pharmaceutical. The catheter is immersed into a saturated solution of a pharmaceutical in a solvent. The saturated solution serves as a swelling agent and swells the polymeric material of the catheter. The catheter is contacted with the swelling agent at or near supercritical pressure and temperature of the solvent. The pressure is then reduced from supercritical pressure to release the solvent from the catheter, thereby leaving the pharmaceutical impregnated within the catheter. There is no description or suggestion of a drug elutably trapped within polymeric material in a predetermined concentration gradient.

The Action cites Col. 3, Lines 27-29 of Greiner for teaching that the "greater the swelling, the quicker and more complete the diffusion of the mixture." The Action concludes from the cited passage that "by saying that the diffusion may not be complete, the polymeric material must have some sort of concentration gradient of pharmacological agent because only a complete diffusion would have an equal concentration within the entire thickness of the polymeric layer." (Action, Page 4). Applicants respectfully disagree with this conclusion.

The passage cited by the Action simply states that speed that a pharmaceutical can be impregnated within a catheter is dependent on the amount of swelling of the catheter material. The fact that not all of a pharmaceutical is impregnated within a catheter does not mean that a concentration gradient of the pharmaceutical has been created in the catheter material. For example, assume that the swelling of the catheter material only allows 75% of a pharmaceutical to be impregnated within the catheter material. The fact that only 75% of the pharmaceutical is impregnated says nothing about how (*i.e.*, concentration gradient) the pharmaceutical is impregnated within the catheter material.

Accordingly, Greiner fails to teach or suggest all of the recitations of independent Claim 73. Applicants respectfully assert that the rejections of independent Claim 73, and all claims depending therefrom, under 35 U.S.C. §103 are overcome.

Independent Claim 88

Independent Claim 88 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Greiner. Amended independent Claim 88 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises *non-layered* polymeric material;

placing the intraluminal prosthesis within a pressure vessel;

pressurizing the interior of the pressure vessel with an inert gas to a predetermined pressure, wherein the inert gas is selected from the group consisting of helium, nitrogen, and argon;

supplying a mixture of a carrier fluid and a pharmacological agent into the pressure vessel;

exposing the *non-layered* polymeric material and the mixture of carrier fluid and pharmacological agent in the pressure vessel for a time such that the carrier fluid and pharmacological agent at least partially penetrate the *non-layered* polymeric material; and

releasing the pressure in the pressure vessel over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the *non-layered* polymeric material and the pharmacological agent becomes elutably trapped within the *non-layered* polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the *non-layered* polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Greiner, as discussed above, fails to teach or suggest a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient. Thus, for at least the same reason that Greiner fails to teach or suggest all of the recitations of independent Claim 73, as discussed above, Greiner fails to teach or suggest all of the recitations of independent Claim 88. As such, Applicants respectfully assert that the rejections of independent Claim 88, and all claims depending therefrom, under 35 U.S.C. §103 are overcome.

Independent Claim 99

Independent Claim 99 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Igaki in view of Guruwaiya. Amended independent Claim 99 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises *non-layered* polymeric material;

immersing the intraluminal prosthesis in a mixture of a carrier fluid and first and second pharmacological agents;

pressurizing the mixture of carrier fluid and pharmacological agents for a time sufficient to cause the carrier fluid and the first pharmacological agent to at least partially penetrate the first unmasked portion and to cause the carrier fluid and the second pharmacological agent to at least partially penetrate the second unmasked portion; and

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the *non-layered* polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution profile of a respective pharmacological agent from the *non-layered* polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

As discussed above, Igaki fails to teach or suggest a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient. Igaki describes controlling the release time point and quantity of an impregnated drug, not via a concentration gradient, but via the use of layers of biodegradable polymer material. Igaki specifically states "by providing the layer(s) of the drug-containing biodegradable polymer in this manner, one or more drugs may be impregnated in the stent, and it is possible to permit more strict control of the drug releasing time point or the quantity of the released drug, or different drugs can be released at the desired same time point." (Igaki, Para. 0072). Igaki also describes retarding the rate of release of a drug impregnated in a stent via the use of a layer of biodegradable polymer material not containing a drug. (Igaki, Para. 0073).

One skilled in the art would not, upon reading Igaki, produce a non-layered stent with a drug concentration gradient in the stent material. To the contrary, one skilled in the art, upon reading Igaki, would use various layers to accomplish what Applicants

accomplish via a concentration gradient. The fact that Igaki utilizes layers to control the time of drug release and the quantity of drug release illustrates that Igaki does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

As discussed above, the secondary reference, Guruwaiya, fails to rectify the deficiencies of primary reference, Igaki. Guruwaiya describes a method for coating a stent that requires the sequential application of three layers of different materials onto a stent's surfaces. A first layer is applied to all or to selected surfaces of a stent and serves as a base or primer coat which readily adheres to the material of which the stent is constructed and in turn, is able to attract and retain the subsequently applied pharmacological agent. Such pharmacological agent, in the form of dry, micronized particles is dusted directly onto all or onto only selected surfaces of the base layer coated stent to form a second layer. A membrane forming polymer is subsequently applied over the coated stent surfaces wherein such polymer is selected for its ability to permit the diffusion of the pharmacological agent therethrough. (Col. 2, Lines 21-34). The amount of pharmacological material deposited in the second layer determines the total dosage that can delivered while the thickness of the top layer determines the rate of delivery. (Col. 2, Lines 45-48). Thus, Guruwaiya does not teach or suggest producing a non-layered stent with a drug concentration gradient elutably trapped within the stent material. Furthermore, the fact that Guruwaiya utilizes a layer to control the rate of drug delivery illustrates that Guruwaiya does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

The Action states that Guruwaiya teaches a method of coating a pharmacological agent on a stent wherein certain portions of the stent are masked during the coating process. (Action, Page 3). The Action then concludes that it would have been obvious to have masked certain portions of the stent of Igaki. (Action, Page 3). However, to the extent that the combination of Igaki and Guruwaiya teaches masking the stent of Igaki, such a combination fails to teach or suggest the following recitations of independent Claim 99:

masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises *non-layered* polymeric material;... and

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the *non-layered* polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution profile of a respective pharmacological agent from the *non-layered* polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Accordingly, Igaki and Guruwaiya, alone or in combination, fail to teach or suggest all of the recitations of independent Claim 99. Applicants respectfully assert that the rejections of independent Claim 99, and all claims depending therefrom, under 35 U.S.C. §103 are overcome.

Dependent Claims 85 and 97

Dependent Claim 85 recites the method of Claim 73, wherein the non-layered polymeric material is non-erodible. Dependent Claim 97 recites the method of Claim 88, wherein the non-layered polymeric material is non-erodible. The Action states that Claim 85 is unpatentable over Igaki in view of Mehta. Applicants respectfully disagree.

Igaki fails to teach or suggest a drug elutably trapped within non-layered, non-erodible polymeric material. Igaki describes a stent formed of a biodegradable polymer material that becomes swollen so as to be impregnated with a drug. When the stent is implanted within a blood vessel, the impregnated drug is released with progress in the degradation of the biodegradable polymer material. (Igaki, Para. 0066). As such, biodegradable polymer material is essential to the Igaki stent. Even if Mehta were to teach non-erodible material, the combination with Igaki would destroy the function of Igaki since Igaki requires biodegradable polymer material. Accordingly, it would not have been obvious to one of ordinary skill in the art to have used a biostable polymer in the process of making the stent of Igaki.

The Action also states that Claims 85 and 97 are unpatentable over Greiner in view of Mehta. As discussed above, Greiner fails to teach or suggest a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient. Greiner describes a method of impregnating a catheter, made of polymeric material, with a pharmaceutical. The catheter is immersed into a saturated solution of a pharmaceutical in a solvent. The saturated solution serves as a swelling agent and swells the polymeric material of the catheter. The catheter is contacted with the swelling agent at or near supercritical pressure and temperature of the solvent. The pressure is then reduced from supercritical pressure to release the solvent from the catheter, thereby leaving the pharmaceutical impregnated within the catheter. There is no description or suggestion of a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient.

As discussed above, Mehta describes deposition of a coating by altering the temperature and pressure of a SCF in which a drug or polymer to be coated is dissolved. One skilled in the art would not, upon reading Mehta, produce a non-layered, non-erodible stent with a drug concentration gradient in the stent material. Moreover, one skilled in the art

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would not, upon reading Mehta, be motivated to modify Greiner to produce a non-layered, non-erodible stent with a drug concentration gradient in the stent material.

Accordingly, dependent Claims 85 and 97 are independently patentable.

Conclusion

In view of the above, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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